Summary of Product Characteristics (SmPC)

1.0 Name of the Medicinal Product

1.1 Product Name

Generic Name: Sitagliptin 50 mg & Metformin Hydrochloride 1000 mg

Trade Name: Silinor-M 50/1000

1.2 Dosage Strength

Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate INN 64.25 mg and Metformin Hydrochloride BP 1000 mg.

1.3 Dosage Form

Oral Solid Tablet

2.0 Qualitative and quantitative composition

Materials	Specification	Function	Unit Formula
Sitagliptin Phosphate (Monohydrate)*	In-house (INN)	Active	64.25 mg
Metformin Hydrochloride*	BP	Active	1000.00 mg
Microcrystalline Cellulose (Type 101)*	USNF	Diluent	42.00 mg
Maize Starch	BP	Diluent	37.50 mg
Povidone (PVP K 30)	BP	Binder	25.00 mg
Sodium Starch Glycolate	BP	Disintegrant	50.00 mg
Sodium Lauryl Sulphate	BP	Surfactant	12.50 mg
Magnesium Stearate	USNF	Lubricant	12.50 mg
Colloidal Anhydrous Silica	BP	Glidant	6.25 mg
Instacoat Aqua-III Brown A03R00114	In-house (Ph. grade)	Coating agent	62.50 mg
Purified Water**	USP	Solvent	q.s

*Quantity may vary depending upon the potency variation of Sitagliptin Phosphate (Monohydrate) INN and Metformin Hydrochloride BP.

** It disappears during coating and does not appear in the finished product.

3.0 Pharmaceutical Form

Silinor-M Tablet 50/1000 are a brown coloured, oblong shaped film coated tablet one side break line and other side plain which is packed in a Blister.

4.0 Clinical Particulars

4.1 Therapeutic Indications

Silinor-M® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Sitagliptin and Metformin is appropriate.

4.2 Posology and method of Administration

Dose of this combination should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg Sitagliptin and 2000 mg Metformin. Sitagliptin/Metformin combination should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to Metformin. The recommended starting dose in patients not currently treated with Metformin is 50 mg Sitagliptin/500 mg Metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with Metformin. The starting dose in patients already treated with Metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of Metformin already being taken. For patients taking Metformin 850 mg twice daily, the recommended starting dose of this combination is 50 mg Sitagliptin/1000 mg Metformin hydrochloride twice daily.

4.3 Contraindication

Combination (Sitagliptin/Metformin) is contraindicated in patients with: Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels 1.5 mg/dL [males), 1.4 mg/dL [females]. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. History of serious hypersensitivity reaction to the combination or sitagliptin, such as anaphylaxis or angioedema.

4.4 Special warnings and precautions for use

Do not use the combination of Sitagliptin & Metformin in patients with hepatic disease. Before initiating the combination and at least annually thereafter, assess renal function and verify as normal. May need to discontinue the combination and temporarily use insulin during periods of stress and decreased intake of fluids and food as may occur with fever, trauma, infection or surgery.

4.5 Interaction with other medicinal products and other forms of interaction

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine,triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Co-administration of Digoxin and Sitagliptin may slightly increase the mean peak drug concentration of Digoxin. But no dosage adjustment of digoxin or Sitagliptin is recommended.

4.6 Pregnancy, nursing mothers

Pregnancy: Pregnancy Category B. The combination of Sitagliptin & Metformin should be used during pregnancy only if clearly needed.

Nursing Mothers:It is not known whether Sitagliptin is excreted in human milk.

Geriatric Use: Because Sitagliptin and Metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, combination of Sitagliptin and Metformin should be used with

caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.
Pediatric Use: Safety and effectiveness of Sitagliptin/Metformin in pediatric patients under 18 years of age have not been established.

4.7 Effects on ability to drive and use machines

Silinor M 50/500 mg has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have beenreported with sitagliptin.

4.8 Undesirable effects

The most common (>5%) adverse reactions due to initiation of Metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinicalstudies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtainingan electrocardiogram), and institute supportive therapy if required.

5.0 Pharmacological Properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose loweringdrugs, ATC code: A10BD07
Silinor M Tablet 50/500 combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin

Mechanism of action

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of

two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma agonists, alpha-glucosidase inhibitors, and amylin analogues. In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Metformin

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake andutilisation
- by delaying intestinal glucose absorption.
- Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

5.2 Pharmacokinetic properties

Silinor M 50/1000

A bioequivalence study in healthy subjects demonstrated that the Silinor M 50/500 (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Silinor M 50/1000.

Sitagliptin

Absorption
Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 M/hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.
Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly boundto plasma proteins is low (38 %).

Biotransformation
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine. Following a [^{14}C]sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contributionfrom CYP2C8.
In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance wasapproximately 350 mL/min.
Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may

also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 □M) or p-glycoprotein (up to 250 □M) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Metformin

Absorption

After an oral dose of metformin, T_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 μg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63 – 276 L.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

No animal studies have been conducted with Silinor M.

In 16-week studies in which dogs were treated with either metformin alone or

a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6.0 Pharmaceutical Particulars

6.1. List of excipients

-Microcrystalline Cellulose (Type 101)
-Maize Starch
-Povidone (PVP K 30)
-Sodium Starch Glycolate
-Sodium Lauryl Sulphate
-Magnesium Stearate
-Colloidal Anhydrous Silica
-Instacoat Aqua-III Brown A03R00114
-Purified Water

6.2. Incompatibilities

None

6.3 Shelf life

2 years (24 months)

6.4 Special Precaution for storage

Store at temperature not exceeding 30ºC in a dry place. Protect from light & moisture.

6.5 Nature and contents of container

Silinor-M Tablet 50/1000 are a brown coloured, oblong shaped film coated tablet one side break line and other side plain. Each tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate (Monohydrate) INN and Metformin Hydrochloride BP 1000 mg as active substances. Each blister contains 8 tablets and inner each carton contains 3 blisters i.e. (3 X 8's).

6.6 Special precautions for disposal and other handling

No special requirements

7.0 Registrant

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9.0 Date of revision of the text

To be stated at the time of printing.

10.0 Dosimetry (if applicable)

Not applicable

11.0 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not applicable